REMARKS

Claims 1 – 9 were pending. All claims were objected to based on the use of unacceptable transitional phrases. All claims were also rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,756,067 to Redgrave.

The claims have been amended so that they are now consistent with Applicant's **granted** European Patent No. EP 1563311. Therefore, for that reason, and for the reasons set forth below, Applicant requests reconsideration of the rejection and the objection. In an effort to advance this matter, the Examiner is also invited to call the undersigned counsel for Applicant at 248-647-6000 prior to the issuance of any future Office action to any potential areas of disagreement.

The Objection

Claims 1 – 9 have been canceled. Therefore, Applicant requests that the objection be withdrawn.

35 U.S.C. 102(b)

The Office action asserts that all claims of application 10/535,230 are anticipated by Redgrave et al. (5, 756,067).

The patent of Redgrave et al. relates to a **method diagnosing presence of or propensity for atherosclerosis and coronary artery disease**. Currently the risks of developing these diseases are assessed by determining cholesterol, triglycerides and lipoproteins in plasma. Plasma levels of these parameters may still be in normal range in patients when an angiographic evidence of atherosclerosis is already documented. Improved diagnostic indicators are needed.

The inventive idea of Redgrave et al. is based on the fact that the transport of fat is carried out in form of triacylglycerol by chylomicrons. In the bloodstream these particles loose

70 % of their triglycerides due to attack of lipoprotein lipases. The resulting particles, the chyloremnants, still containing the whole amount of the chylomicrons cholesterylester, transport cholesterol from the intestine to the liver. The inventors predict that the clearance rate of chyloremnants would be a diagnostic tool for assessing a patient's ability to develop atherosclerosis and for monitoring effectiveness of therapies by repeated measurements at intervals of weeks or months.

Concentrations of chylomicrons and chyloremnants are difficult to measure because of their short half-life, their low concentrations in relation to other lipoproteins, and their non-unique composition. Therefore, Redgrave et al. simulate the exogenous lipoprotein transport by artificially introducing isotopically tagged diagnostic compositions into test subjects. The particles of these compositions imitate chyloremnants with respect to their size and chemical structure. They have a diameter from 20 -2000 (150) nm and consist of triglycerides, phospholipides, cholesterol and cholesterylesters, one of which has a stable isotopic tag. Stable isotope tagging includes but is not limited to 13 C, tritium or the radioisotope 14 C. All components of the diagnostic composition are metabolised by normal physioplogic pathways. **The to the tagged component corresponding tagged metabolite** is quantified by liquid scintillation or mass spectrometry in a patient's blood, urine, or expired air in intervals over a period of several hours. Redgrave et al. suppose that the amount of the successfully metabolised tagged component over a unit of time is a measure for the rate of the metabolic turnover of chyloremnants and hence directly related to a patient's metabolic predisposition to develop atherosclerosis and coronary artery disease. Reduced chyloremnant clearance indicates increased risk.

The above developments deal with **isotopically tagged molecules** for the purpose to **simulate features of an exogenic lipoprotein transport system** in order to assess amounts and rates of metabolic turnover.

On the other hand the method of enteral labelling is employed, when **adulteration of samples** gets a problem in the **analysis of drugs of abuse, intoxicants or doping substances**. The problem is approached by labelling a patient's urine with marker substances which are administered orally prior to the delivery of urine. These marker substances are **not metabolisable**, after a short time elapsed they appear unchanged in urine and are thus **unequivocally providing an identification of the sample in relation to the sample donor**. The main target of these **developments is to offer methods which allow to collect urine without the obligatory supervision**.

The instant application is a supplementary development of the application of Keller et al, (10/471,815), where the authenticity markers are chosen from low-molecular-mass polyethylene glycols,

Some patients tried to avoid the detection of illicit drugs by spitting marker substances into "clean" methadone containing urine. At this point the present application comes into use. Substances had to be included in the marker solution which would be **metabolised** in contrast to polyethlene glycol and which would be identifiable but not normally present in urine. If a patient should attempt to manipulate the allocation by contaminating the urine with the marker substances, the presence of the metabolisable substance there makes a **fraudulent falsification reliably recognisable**. These substances are monitoring patient compliance. Advantageous compliance markers are the substances listed in claims 4-5.

All claims are rejected in the Office action. The rejection of **claims 1-3** as allegedly being unpatentable over Redgrave et al. is respectfully traversed. Contrary to the Examiner's assertion, Redgrave et al. cannot be cited as relevant background art reference. Their developments are far apart from and not in any way related to the method of enteral labelling as the above short description of their invention, simulating an exogenous lipoprotein transport particle, may disclose. Redgrave et al. use the term labelling when they tag a molecule with radio or mass isotopes. Their labels **are single atoms, which discriminate one metabolisable substance among other metabolisable substances** within a particle of the diagnostic composition, Redgrave et al. are not using marker substances as used in the instant application, which, as a supplementary development of Keller et al., labels samples with mixtures of not-metabolisable and **additionally metabolisable marker substances** in order to assign unambiguously test results to sample donors and **additionally to disclose deceptive manipulation of sample results**. If the combination of the not-metabolisable markers is correctly detected and the metabolisable marker is not present, then the urine sample is investigated for the analytes of interest (drugs, intoxicants, doping substances).

The rejection of **claims 4 and 5** as allegedly anticipated by Redgrave et al. is respectfully refused. Neither in the abstract, nor in the examples 1 -3, nor in the written description, nor in the claims benzoic acid derivatives are even mentioned. Thus Redgrave et al. cannot be cited against the novelty of these claims. Moreover, contrary to Redgrave et al., the used metabolisable marker substances are **not normally identifiable in body excretions** (urine), and that is the **prerequisite in the nature of the method, the most essential condition**. They are only present

and thus identifiable in urine, when a test person has contaminated the sample with marker drinking solution.

The rejected claims 6-9 are cancelled, following the Examiner's proposal.

The attributes of ideal marker substances are described in detail in the instant application (page 1 [0012] to page 2 [0015]). It is very difficult to find substances realising all these assumptions. Best suitable as compliance marker is the substance **methyl-4-hydroxybenzoate (MHB)**. It is registered as preservative for foods and may be used, when enteral labelling is applied to the methadone projects, for **conserving of the methadone drinking solution**. Thus the substance fulfils an important function in the technical procedure of enteral labelling and no additional burden for the test subjects and no additional costs arise.

Most desirably the MHB marker behaves during chromatography similarly to the PEG markers so that it can be **characterised together with them in the same chromatogram**. For the first time in enteral labelling, authenticity and compliance markers can be determined in the same analysis. MHB is identifiable phenomenologically within the characteristic chromatographic pattern of the PEG markers, even by untrained persons. They only have to decide about the presence or absence of the corresponding analytical signal.

Currently patient compliance is monitored with altogether at least 3 analyses for every tested person, one for characterising authenticity marker substances and at least two for monitoring patient compliance. By introduction of the MHB marker, instead of these three analyses only one would have to be carried out, and that would be of great benefit for the commercial exploitation of enteral labelling with PEG authenticity markers. Notable reduction of costs would be obtained with respect to qualified personal, reagents, materials, and last but not

least to waste avoidance from disposables. Technical simplification of the analytical procedure would be achieved. Besides HPLC equipment, no additional analyser is required. Overall time of analysis is shortened. Work instructions get an easy-to-read format, concise and clear.

From these points of view, MHB and similar benzoic acid derivatives are most advantageous and most convenient compliance markers for enteral labelling in combination with low- molecular-mass PEGs as authenticity markers. Applicant would like to signalise that she does not claim novelty to the already known method of enteral labelling, as is pointed out in the two-part form of claim 1, but requires examination for novelty to the compliance markers, comprising benzoic acid derivatives. These have not been employed before as marker substances in enteral labelling.

In view of the above amendment, Applicant submits that the pending application is now in condition for allowance.

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Respectfully submitted,

By _____

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